# The Lifecourse Consequences of Very Preterm Birth

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**Keywords**: very preterm birth, cognitive development, mental health, quality of life, wealth, romantic relationships, developmental models,

**Acknowledgements:** We would like to thank Yiwen Liu for her assistance in proof reading and figure production. Dieter Wolke and Samantha Johnson are partly supported and Marina Mendonca fully supported by funding from the European Union's Horizon 2020 Research and Innovation Program RECAP Preterm (grant 733280). Dieter Wolke received additional support from the Norface Dial program (grant 462-16-040). The funders had no role in the preparation, approval or submission of the manuscript.

**List of Abbreviations used in text**

| Abbreviation | Meaning | Definition |
|---|---|---|
| EP | Extremely preterm | Variable; ranging from gestation <28 weeks or <26 weeks |
| VP | Very preterm | <32 weeks of gestation |
| MP | Moderate preterm | 32-33 weeks of gestation |
| LP | Late preterm | 34-36 weeks of gestation |
| Term | Term | ≥37 weeks of gestation |
| NBW | Normal birthweight | Birthweight >2499 g |
| LBW | Low birthweight | Birthweight <2500 g |
| VLBW | Very low birthweight | Birthweight <1500 g |
| ELBW | Extremely low birthweight | Birthweight <1000 g |
| AGA | Appropriate for gestational age | The foetus/newborn has a weight corresponding to his gestational age (e.g. above the 10th percentile on standard weight charts) |
| SGA | Small for gestational age | The fetus/infant has a weight below that expected for his gestational age (e.g. below the 10th percentile on standard weight charts) |

**Abstract**

Around 15 million children are born preterm (<37 weeks' gestation) every year. Of these, 15% or 2.25 million are born very preterm (VP; <32 weeks' gestation). Only in the last 5 decades, with the advent of coordinated neonatal intensive care, have VP babies survived and we are beginning to understand more about the long term impact of birth at VP gestations. Here their developmental outcomes in diverse domains from motor, cognitive, and social function to mental health and wellbeing throughout childhood and adolescence are reviewed. Furthermore, their life course adaptation in terms of romantic relationships, employment and quality of life into adulthood are considered. For some domains of functioning, the differences from term-born born peers are large (e.g. IQ), but for others they are moderate (e.g. academic achievement) or small (e.g. anxiety), and in others the risk is reduced such as for risk-taking behavior. Some adverse effects reduce across age and others remain remarkably stable from childhood into adulthood. We argue that to advance understanding of developmental mechanisms and to direct resources for intervention more effectively, social factors need to be assessed more comprehensively, genetic sensitive designs should be considered with neuroimaging integrated to test alternative developmental models. As current evidence is based almost exclusively on studies from high income countries, research from low and middle income countries is urgently needed.

**Contents**

## INTRODUCTION

To achieve the United Nations' Sustainable Development Goal 3 to ensure healthy lives and promote wellbeing for all at all ages, it is crucial to address the global burden of preterm birth (Chawanpaiboon et al 2019). In 2014, 10.6% of live births or 14.84 million babies were born preterm, before 37 weeks of gestation, worldwide. Preterm birth is the leading cause of under-5 child mortality (Lee et al 2019). In the last three decades, the largest improvement in survival has been for babies born very preterm (VP), before 32 weeks of gestation. Although VP births account for only 15% of all preterm births, they are associated with the highest costs both for initial hospitalisation (Petrou et al 2019) and for health and educational support in the long term (Petrou et al 2013). As up to 95% of VP babies now survive in high income countries, focus has shifted from solely reducing mortality to understanding and improving long term outcomes and quality of life. Here we provide an overview of the lifecourse consequences of VP birth and of the developmental mechanisms leading to adverse motor, psychological and social outcomes.

## TERMINOLOGY AND EPIDEMIOLOGY

The World Health Organization defines preterm birth as all births before 37 completed weeks of gestation. The limit of viability is currently around 22 weeks, but survival at this gestational age is still rare. About 3.3%-8.9% of all preterm babies are born extremely preterm (EP; <28 weeks' gestation) and about 9.8%-12.8% at 28-31 weeks of gestation, with all infants born before 32 weeks classified as very preterm (VP) (Chawanpaiboon et al 2019). Up to 20% of preterm babies are born moderately preterm (MP; 32-33 weeks' gestation) and 60%-70% late preterm (LP; 34-36 weeks' gestation (Goldenberg et al 2008).

The terms ‘preterm’ and ‘low birthweight’ (LBW; <2500g) are often used interchangeably in studies of the long term outcomes of these infants. Approximately 7%-10% of all babies are born with LBW (Wolke, 1991) and around 0.9%-1.5% with very low birthweight (VLBW; <1500g). Extremely low birthweight (ELBW) infants are usually labelled as such if born <1000g (Hille et al., 2001) or sometimes <750g/<800g (Whitfield et al 1997).

Appropriate for gestational age (AGA) and small for gestational age (SGA) infants are classified based upon the relationship between gestation and birthweight using standard population or customised birthweight growth charts (Zeitlin et al 2017). SGA children are born <$10^{th}$ or <$3^{rd}$ percentile or ≤2 standard deviations below the mean for their gestational age (Zeitlin et al 2017). Within the preterm population, 16%-40% of babies are born SGA (<$10^{th}$ percentile).

In absolute numbers, most preterm babies are born in Asia (52.9% of global preterm births) and Sub-Saharan Africa (28.2%). In contrast, Europe (4.7%) and the USA (3.3%) account just for a small fraction of the global burden (Chawanpaiboon et al., 2019).

Preterm labor may be spontaneous (due to spontaneous preterm labor or pre labor rupture of membranes) or clinician initiated (cesaerian section or induction of labor) due to maternal or fetal indications such as infection, poor fetal growth or high blood pressure (Goldenberg et al 2008). Factors associated with preterm delivery include sociodemographic (e.g. race, poverty), nutritional (e.g. obesity), maternal genetic or microbiome , environmental (e.g. smoking) and lifestyle factors (e.g. fertility treatment, increasing maternal age)but still in 50% of cases the specific cause is unknown (Muglia & Katz 2010).

The number of VP births has not significantly decreased, and has even increased in many countries, whilst mortality rates have decreased, at least in high and middle income countries (Yeo et al 2015). As such, the absolute number of survivors born VP is increasing, presenting a growing public health concern.

## DEVELOPMENT AFTER VERY PRETERM BIRTH

This review focusses on motor, psychological and social development from infancy to adulthood following VP birth. Thus the major organ considered is the brain. Whenever possible, the focus will be on high quality studies that: (a) are prospective; (b) are sufficiently powered (e.g., geographical, epidemiological, or multicentre studies); (c) have few infants lost to follow up or good documentation of dropouts; (d) include full term control groups for cohort specific comparisons; (e) are long term (i.e., into school age or adulthood); (f) include differential reports of sub-populations (e.g., social class, EP vs. VP); and (g) are conducted by independent researchers not involved in the care of the infants under investigation and blind to study group allocation (Johnson et al 2008, Vohr 2007). Particular emphasis will be placed on studies using contemporaneous control groups as secular trends in cognitive and behavioural scores have been repeatedly reported (Collishaw et al 2010, Wolke et al 1994). Finally, we focus predominantly on reports of mean differences or differences in proportions between VP individuals and term-born controls and, where possible, refer to meta-analyses to estimate effect sizes.

### Motor Development and Physical Activity

Motor difficulties following VP birthrange from mild delays, such as in sitting or walking, to severe neuromotor impairment, such as cerebral palsy (CP) which remains the primary motor disorder following VP birth (Reid et al 2016). Other deficits in coordination, balance, gross and fine motor control and visual-motor integration are usually referred as motor impairments without CP and may be considered as Developmental Coordination Disorders (DCD) according to DSM-V criteria (American Psychiatric 2013).

Findings from one of the most comprehensive CP registries in Victoria, Australia, indicate that CP rates have decreased since the mid-1990s in those born VP (28-31 weeks' gestation), from 41.5/1000 neonatal survivors (NNS) in 1983-1991 to 32.4/1000 in 2001-2009 (Reid et al 2016). In contrast, among EP births, CP rates increased until 2000 with a decrease thereafter (92.1; 102.5 and 70.6/1000 NNS in 1983-1991, 1992-2000 and 2001-2009, respectively). Although VP/EP births are just 1%-2% of all births, they make a large contribution to the rates of children with CP. The improvements for VP/EP births may be due to considerable change in the management of preterm infants over recent decades, but there is little evidence for the efficacy of any single intervention in reducing CP rates (Spittle & Orton 2014).

Regarding motor impairments without CP , children born VP/VLBW had scores -0.57 to -0.88 SD lower than term-born peers on standardised tests of motor performance from infancy to 15 years of age (de Kieviet et al 2009). These differences were of a moderate to large effect size and were found in a wide range of skills including balance, ball skills, manual dexterity, and fine and gross motor development. Whilst motor skills improved from infancy to childhood, no significant improvement was found from childhood into adolescence. A more recent review excluding children with CP (Edwards et al 2011) found a higher risk for DCD in VP/VLBW children with OR 6.29 (95% CI 4.37, 9.05) and OR 8.66 (95% CI 3.40, 22.07) for scoring <5th or 5$^{th}$-15$^{th}$ percentile on the MABC, respectively. Even larger differences of 1.1 to 1.6 SD have been found among children born <26 weeks of gestation (Marlow et al 2007).

A major question remains whether DCD has decreased with improved neonatal care. The Victorian Infant Collaborative Study (VICS) in Melbourne, Australia, recruited 3 consecutive cohorts of EP/ELBW babies born in 1991-1992, 1997 and 2005 from 4 tertiary neonatal units in the region (Spittle et al 2018). Whilst survival rates increased from 54% in 1991-1992 to 68% in 1997 and stabilized in 2005 at 64%, CP rates remained constant at 11%, 11% and 12% respectively. In contrast, non-CP motor impairment increased over time despite advances in neonatal care, with a prevalence of 13%, 15% and 26% among EP/ELBW children respectively (Spittle et al 2018). Although there were consistent independent perinatal predictors of motor impairment across the 3 epochs, including poorer fetal growth, brain injury, surgery, and male sex, these did not explain the increased rate of motor impairment in the 2005 cohort. The authors speculated that other factors such as reduced physical activity (PA) may have adversely impacted on motor outcomes in the EP/ELBW children.

Indeed, one might expect that VP/EP children participate less in sports and PA given the higher rate of motor impairments. However, according to WHO recommendations, individuals born preterm are encouraged to participate in PA to improve lung function and cardiovascular fitness (Spiegler et al 2019a). Indeed, a recent longitudinal study from birth to 14 years show that VP children and adolescents did not engage less in PA or sport than term-bon controls. Rather PA was higher in male adolescents, those of white ethnicity, higher parental education, having been taken to live sport events at 5-7 years or having taken part in organized PA at 5-7 years (Spiegler et al 2019b). Thus, consistent with other studies, VP children are not less likely to be physically active but they reduce participation in sport by adolescence just as term-born children do.

**Cognitive Development**

A recent meta-analysis of 71 identified that VP/VLBW individuals had IQ scores 0.86 SD (95% CI: -0.94, -0.78) lower than controls at age 5-20 years, equating to a 12.9 point deficit (Twilhaar et al., 2018b). Similar effect sizes have been reported in other meta-analyses with deficits of 10.9 (95% CI 9.2, 12.5) (Bhutta et al 2002) and 11.9 (95% CI 10.47, 13.42) IQ points in all preterm children compared with controls. Among VP cohorts, a mean deficit of 13.9 (95% CI 11.5–16.2) IQ points has been reported (Kerr-Wilson et al 2012). Together these studies indicate that IQ in VP individuals is, on average, 0.7 to 0.9 SDs lower than term-born peers.

In two meta-analyses the mean difference in IQ did not differ significantly over time, suggesting that cognitive outcomes have not improved significantly despite advances in neonatal care (Kerr-Wilson et al 2012, Twilhaar et al 2018a). The only direct comparison of IQ in consecutive cohorts from the same geographical region is from the VICS group for EP/ELBW babies born in 1991-1992, 1997 and 2005. Similar to the findings for CP outlined above, they found that the mean difference in IQ between EP children and controls was not significantly different for births in 2005 compared with births in the 1990s at age 8 years. Similarly there was no significant difference in the proportion with cognitive impairment (IQ < -2 SD of controls) (Cheong et al 2017). Thus, despite improved neonatal care and reduced prevalence of severe neurosensory disabilities (Doyle et al 2010), there is no evidence yet of improved cognitive outcome over time.

Notably, all meta-analyses found a significant association between IQ and gestational age (Allotey et al 2018, Bhutta et al 2002, Kerr-Wilson et al 2012, Twilhaar et al 2018a) indicating a dose-response effect of gestation at birth on cognitive outcome. This association has also been shown in large population-based studies (Poulsen et al 2013, Wolke et al 2015b), however it is not yet clear whether this is a linear association among birth at all preterm gestations (Bhutta et al 2002, Kerr-Wilson et al 2012) or an exponential relationship with increasing deficit observed in those born before 32 weeks of gestation (Jaekel et al 2013, Wolke et al 2015b). It is clear however that those born EP (<26 weeks gestation) are at highest risk for impairments with deficits of 1.3 to 1.6 SD in IQ at 11 and 6 years of age, respectively (Johnson et al 2009, Marlow et al 2005).

A key question is whether cognitive deficits observed in early childhood persist across the lifespan or whether VP individuals catch up to their peers as they age. Meta-analyses have typically found that mean differences in IQ do not narrow with age (Allotey et al 2018, Twilhaar et al 2018a). However, these are based on successive cross-sectional comparisons rather than an analysis of developmental trajectories across time.

Studies that have tracked the development of VP/VLBW/EP individuals from birth through adulthood have failed to find evidence of developmental catch-up. The EPICure Study assessed IQ in EP children at 2.5, 6, 11 and 19 years of age alongside a term-born control group assessed from 6 years of age. Deficits in IQ remained stable over time although there was a small but statistically significant narrowing of the gap by 0.5 IQ points per year and an 18-point deficit remained at 19 years of age (Linsell et al 2018). Similar results have been reported for VLBW/VP survivors who had significantly lower IQ than term-born controls when assessed at 2, 4, 6, 8 and 26 years of age (Breeman et al 2015).

Compared with IQ, there are fewer reports of attention and executive functions to date. Meta-analyses have found small to moderate deficits for verbal fluency (-0.57 SD), working memory (-0.36 SD), and cognitive flexibility (-0.49 SD) in VP children compared with controls (Aarnoudse-Moens et al 2009). Standardised mean differences of -0.42 to -0.71 for working memory and -0.35 to -0.62 for processing speed have also been reported in preterm children compared with controls (Allotey et al 2018). Similar effect sizes have been reported in VP children who had scores 0.51 SD (95% CI -0.58, -0.44) lower than controls on 87 measures of executive functions and 0.49 SD (95% CI –0.60, -0.39) lower on tests of processing speed (Brydges et al 2018). Significant deficits have also been observed in VP cohorts in adulthood (Eryigit Madzwamuse et al 2015), however, these are usually smaller in size than deficits in IQ. Similar to the findings for IQ, there is no evidence of improved executive functions with improved neonatal care since the 1990s (Burnett et al 2018).

**Schooling and academic attainment**

In meta-analyses of performance on standardised achievement tests, preterm born children have scores 0.71 to 0.78 SD lower than term-born controls in mathematics, 0.44 to 0.67 SD lower in reading, and 0.52 to 0.56 SD lower in spelling (Allotey et al 2018, Twilhaar et al 2018a). In children born VP, mathematic scores have been shown to be 0.60 SD (95% CI -0.74, -0.46) lower than controls, reading scores 0.48 SD (95% CI -0.60, -0.34) lower and spelling scores 0.76 SD (95% CI -1.13, -0.40) lower (Aarnoudse-Moens et al 2009).

Population-based studies have also found a significant dose-response effect of gestation at birth on educational outcomes. Routine data linkage for 407,503 children in Scotland revealed that the risk of SEN increased as gestational age at birth decreased for each week of gestation below 40 weeks, with adjusted OR of 1.16 (95% CI 1.12, 1.20) for children born at 37-39 weeks, OR 1.53 (95% CI 1.43, 1.63) for children born at 33-36 weeks, OR 2.66 (95% CI 2.38, 2.97) for those born at 28-32 weeks, and OR 6.92 (95% CI 5.58, 8.58) for children born at 24-27 weeks (MacKay et al 2010).

A dose-response effect of birth at all gestations prior to term has also been reported in academic attainment (Pettinger et al 2019, Wolke et al 2015b). For example, the proportion of children who failed to reach a good level of achievement at age 7 in school attainment tests increased as gestational age at birth decreased, with 43% of VP children failing to have a good level of achievement in assessment, compared with 18% of children born at full term (RR 1.78, 95% CI 1.24, 2.54) (Chan & Quigley 2014).

VP birth has a pervasive effect on learning with significantly poorer performance in all school subjects. However, marginally greater deficits are found in mathematics compared with other subjects (Aarnoudse-Moens et al 2009, Allotey et al 2018, Twilhaar et al 2018a). This is due to VP children's general cognitive deficits, such as impairments in working memory and visuospatial skills, rather than deficits in numerical skills (Jaekel & Wolke 2014, Simms et al 2015).

Do academic deficits observed in childhood represent a developmental delay or persistent deficits across schooling? Twilhaar and colleagues found no significant differences in the trajectories of VP children and term-born controls in arithmetic, reading or spelling throughout elementary school (Twilhaar et al 2018b). Another investigation of results on school attainment tests found that preterm children showed gains in attainment between age 7 and 11, closing the gap slightly with term-born peers, but not at ages 11 and 14 (Odd et al 2019). Thus, overall, preterm children do not catch up with their peers and substantial deficits in achievement are still evident at the end of compulsory schooling.

As with cognitive outcomes, relying on improved neonatal care for improving educational outcomes does not appear to hold the answer. In the VICS cohorts, achievement in reading, spelling and mathematics was significantly poorer in EP children born in 2005 compared with those born in the 1990s (Cheong et al 2017). The reasons for the deterioration in academic performance are not known, but it is clear that improvements in neonatal care need to be paralleled with improved teacher training and educational support for children born preterm (Johnson et al 2015, Pettinger et al 2019).

**Mental Health**

The assessment of mental health in cohort studies has mainly been carried out using parent, teacher or self-completed rating scales rather than costly diagnostic evaluations. A recent meta-analysis using these measures revealed a small to moderate effect for increased internalizing symptoms (Standardized Mean Difference (SMD) 0.42; 95% CI 0.26, 0.58) in EP/ELBW children compared with controls, and a small effect for externalizing problems (SMD 0.15; 95% CI 0.02, 0.28) (Mathewson 2017). An individual participant data meta-analysis of 6 cohort studies in adulthood similarly found higher scores for internalizing problems but lower scores for externalizing problems among VP/VLBW adults compared with controls (Pyhala et al 2017). The effects, however, were usually very small with mean differences in z scores ranging from 0.06 to 0.12.

In childhood a 'preterm behavioral phenotype' (Johnson & Marlow 2011) has been described which is characterised by an increased risk for attention problems, emotional problems, and difficulties with social interaction, alongside no increased risk for aggressive or delinquent behavior (Johnson & Marlow 2011, Mathewson 2017). This was first evidenced by a similar pattern of findings in five cohort studies (Farooqi et al 2007, Hille et al 2001).

At the diagnostic level, a meta-analysis of 5 studies identified an OR of 3.66 (95% CI 2.57, 5.21) for psychiatric disorders in preterm/LBW children and adolescents relative to FT controls, with prevalence estimates that ranged from 21 to 28% (Burnett et al 2011). The pattern of disorders observed in preterm populations indicates an increased risk for Attention-Deficit/Hyperactivity Disorder (ADHD), Depressive and Anxiety Disorders, and Autism Spectrum Disorder (ASD), alongside no increased risk for Disruptive, Impulse-Control or Conduct Disorders (Johnson & Marlow 2011, Johnson & Wolke 2013).

ADHD is the most common disorder after VP birth for which fairly consistent risk estimates have been reported with ORs of 3.3 (95% CI 2.0, 5.6) (Allotey et al 2018) and 3.04 (95% CI 2.19, 4.21) for ADHD in VP children and adolescents (Franz et al 2018). The odds are even higher for those born EP/ELBW (OR 4.05; 95% CI 2.38, 6.87) (Franz et al 2018). VP children with high levels of ADHD symptoms show wide-ranging cognitive deficits (James et al 2018, Retzler et al 2019) which might also account for the comorbidity of psychiatric disorders in this population. In particular, a highly increased risk for ASD has also been reported in VP populations, with a prevalence of 7% among children born VP (Agrawal et al 2018), and up to 8% among those born EP (Johnson et al 2010).

There is good evidence that the increased risk for internalizing symptoms persists into adulthood while externalizing problems are lower than in term-born controls (Mathewson 2017, Pyhala et al 2017, Van Lieshout et al 2018b). However, whilst ADHD diagnoses seem to persist into adulthood (Breeman et al 2016a, Burnett et al 2013), emotional disorders reduce by adulthood (Burnett et al 2013, Jaekel et al 2018a, Johnson et al 2019b). Thus EP/VP survivors may be better emotionally adapted than once anticipated. Whether this is a true decline or due to reduced statistical power resulting from loss from follow-up is not yet clear.

**Social Development**

Parent-Infant Relationship

Despite recent efforts of NICU policies to promote parental involvement and physical proximity as early as possible, infants are often in incubator care for weeks and months, which may impact on maternal attachment formation (Feldman et al 2014). Furthermore, an unexpected preterm birth and the ensuing period of uncertainty over their infants' survival can place high levels of stress on parents (Singer et al 1999). However, parents of preterm infants often learn to cope with the higher stress over the first years of their offspring's life (Schappin et al 2013).

Attachment refers to the emotional bond that the infant forms with consistent caregivers who are sensitive and responsive in their social interactions (Bowlby 1969). Several reviews found no differences in secure-insecure attachment between preterm and term-born children (Field 1987, van Ijzendoorn et al 1992). In particular, maternal sensitivity has been found to be a major factor in predicting secure attachment (Miljkovitch et al 2013, Wolke et al 2014). A recent meta-analysis of 34 studies reported that despite the initial stress and separation, mothers of preterm children were as sensitive in their interactions with their children as mothers of term-born children (Bilgin & Wolke 2015). This suggests that similar maternal sensitivity allows mothers of preterm infants to adapt to and promote sensitive interactions (van Ijzendoorn et al 1992).

While secure and insecure attachment styles are organised patterns of dealing with reunion, disorganized attachment is manifested by contradictory, misdirected or stereotypical behaviors (Carlson 1998) that are associated with child psychopathology (Weinfield et al 2000). Pipp-Siegel and colleagues (1999) have suggested that neurological abnormalities can lead to similar behaviors to those that characterise disorganised attachment styles, usually associated with situations of child abuse or neglect (Pipp-Siegel et al 1999). Indeed, there is evidence that VP/VLBW children are more likely than term-born children to have disorganised attachment. Notably this was predicted by the infant's neurological impairment (distressing cry and developmental delay) and unrelated to parenting (maternal sensitivity) (Wolke et al 2014).

There is some evidence that parents of VP children are more often overprotective than parents of term-born children indicated by being more controlling in mother-infant play interactions, even when excluding children with neurosensory impairment (Forcada-Guex et al 2006, Wightman et al 2007). Similar overprotection has been reported among VLBW adolescents (Indredavik et al 2005) and VLBW young adults (Pyhala et al 2011). Higher parental control behavior and protection for VP children, however, may be partly explained by VP's children's cognitive deficits and functional limitations and additional needs for framing and guidance (Jaekel et al 2012). However, parents' perception about their child's vulnerability appears to depend mostly on parents' psychological factors (e.g. anxiety, parental stress) rather than the child's health (Tallandini et al 2014). Indeed, parental anxiety has been associated with more controlling parenting and children's lower self-efficacy (Schneider et al 2009), which may ultimately impair their resiliency (Schwarzer & Warner 2013).

Peer Relationships

An important aspect of social development is the ability to relate to and form relationships with peers. A systematic review of 23 studies found that VP children and adolescents have higher levels of social withdrawal and peer problems than children born at term (Ritchie et al 2015). Further, studies that included the child's own self-report found that VP children have fewer close friends, spend less time with friends, and are less satisfied with their friendship network than their term-born peers (Heuser et al 2018, Ritchie et al 2018). VP children are also more than twice as likely to be socially excluded and bullied than term-born children and this often persists from elementary to secondary school (Day et al 2015, Ritchie et al 2018, Wolke et al 2015a). Poor peer relationships among VP children are important as they are associated with emotional problems, inattention/hyperactivity, motor deficits (Day et al 2015, Heuser et al 2018, Ritchie et al 2018) and displaying more autistic features, i.e. higher rates of social and communication problems (Williamson & Jakobson 2014). Despite having fewer friends, direct observation of dyadic interactions between friends, one of whom was born preterm, found that friendship activities and behaviors are similar between children born PT and at term , as well as their perceived relationship quality (Ritchie et al 2018, Sullivan et al 2012). It appears that VP children's withdrawn behavior may hinder them in forming and maintaining successful peer relationships.

## ADULT LIFE

### Personality

Compared with term-born controls, adults born VP have been shown to be less extraverted (Eryigit-Madzwamuse et al 2015, Pesonen et al 2008), more agreeable and cautious (Hertz et al 2013, Pesonen et al 2008), more shy and withdrawn (Eryigit-Madzwamuse et al 2015, Johnson et al 2019b), and less prone to criminal and risk-taking behaviors, such as smoking and illicit drug and alcohol use (Eryigit-Madzwamuse et al 2015, Hack et al 2002, Hille et al 2008). VP born adults report higher levels of neuroticism (Allin et al 2006, Eryigit-Madzwamuse et al 2015, Hertz et al 2013) and more autistic features than term-born controls. It is possible that VP adults' socially withdrawn personality or adverse peer experiences makes it more difficult for them to form and maintain social relationships.

**Social relationships**

The social lives of adults born VP have typically been investigated in cohort studies and in Scandinavian registry studies. In a meta-analysis of 21 such studies including 4.4 million participants, preterm/LBW adults were less likely to form romantic partnerships (OR=0.72; 95% CI=0.64 – 0.81), to have had sexual intercourse (OR=0.43; 95% CI=0.31 – 0.61), or to have become parents (OR=0.77; 95% CI=0.65–0.91) compared to adults born at term (Mendonca et al 2019). No differences according to sex or age were found suggesting that individuals born preterm/LBW are more likely not to accomplish these milestones in adult life rather than being delayed in doing so.

Social difficulties are important as they are associated with adverse outcomes (Umberson et al 2010), such as lower wealth, social isolation, and poorer physical and mental health (Jaekel et al 2018a) and they often worry parents (Wolke et al 2017). Prematurity is also associated with a cross-generational fertility loss: not only are adults born preterm less likely to become parents, but their parents were also less likely to have further children after the birth of a preterm child (Alenius et al 2018). Despite having fewer friends (Baumann et al 2016, Darlow et al 2013), the quality of social support from peers was perceived as good in adults born PT/LBW as those born at term. Furthermore, when preterm adults had a romantic partner, the quality of this relationship was perceived slightly more positive than in term-born peers.

**Markers of Wealth**

In a meta-analysis of 23 studies including 5.9 million participants, adults born PT/LBW were found to have lower educational qualifications (OR 0.74; 95%; CI 0.69, 0.80), lower employment rates (OR 0.83; CI 0.74, 0.92), and greater receipt of social benefits (OR 1.25; CI 1.09, 1.42) than adults born at term (Bilgin et al 2018). These associations were consistent across different geographical regions and age, and a dose-response effect of gestational age was found for educational qualifications in which adults MP/LP were 18% less likely than term-born adults to have higher educational qualifications, and VP adults were 40% less likely. Although previous studies reported that preterm adults were less likely to live independently (Baumann et al 2016, Kajantie et al 2008), independent living was not significantly lower in this meta-analysis (Bilgin et al 2018). This may be because Scandinavian countries have a welfare system and cultural practices that support young people's independent living (D'Onofrio et al 2013), hence reducing the adverse impact of preterm birth on transition into adult life. Investigation in other parts of the world is required.

**Quality of life**

Health-related quality of life (HRQOL) refers to the subjective impact of health on an individual's overall psychological, social, and physical well-being (Horsman et al 2003). Rather than having different measures for specific medical conditions (e.g. cancer; rheumatism or very preterm birth), having one measure of HRQOL allows for the comparison of consequences or effects of treatment across all medical conditions. This is of practical importance when difficult decisions have to be reached by budget holders on how to best deploy limited health resources.

A systematic review in 2008 (Zwicker & Harris 2008) identified 15 studies that had compared HRQOL at preschool (6 studies), school age (1), in adolescence (4) and in early adulthood (4) between EP/VP/VLBW individuals and term-born controls. It was found that

HRQOL was lower in individuals born preterm in the preschool years according to parent report. In adolescence, parents reported lower HRQOL for VP/EP/VLBW participants than term-born controls, but no differences were found in self-reports. Furthermore, in early adulthood (18-23 years) no significant differences were found between groups, although EP/VP/VLBW adults tended to report slightly less physical and overall functioning (Zwicker & Harris 2008).

These results need to be interpreted cautiously for a number of reasons. Firstly, different findings were found when parent versus self-reports were used with parents reporting lower HRQOL than the participants themselves (Baumann et al 2016, Zwicker & Harris 2008). Consistent with social comparison theory, parents may take a wider view of their offspring compared to all same-aged peers, while their offspring may compare themselves to a selection of same-aged peers they interact with. Secondly, studies that only include self-report exclude those with severe neurosensory impairment (NSI) who are less likely to be able to complete these scales. This introduces bias in favour of no group differences. Thus studies should include both self-report and parent report (Baumann et al 2016). Thirdly, whole population studies of VP survivors have loss to follow-up, with those with NSI, socially deprived and from ethnic minorities more likely to drop out (Hille et al 2005, Wolke et al 1995, Wolke et al 2009). These groups are more likely to have lower HRQOL (Wolke 2016). Fourthly, the various measures of HRQOL are very different in their scaling. Some just add items in subscales while others determine utilities (i.e. multi-attribute utility scores that represent mean community preferences ranging from 0.00 (rather be dead) to 1.00 (perfect health). Thus comparisons of studies are strictly only possible if the same measures are used. Finally, level of HRQOL is influenced by variations in neonatal treatment philosophy across different region (Breeman et al 2016b), by cultural differences and the general happiness of the nation (Verrips et al 2008).

Wolke (Wolke 2016) compared ELBW/VP/VLBW survivors from three population studies in Germany (Baumann et al 2016), Netherlands (van Lunenburg et al 2013) and Canada (Saigal et al 2016) who had followed children into adulthood and used the identical measure. The weighted for all ELBW (with and without NSI) participants was significantly lower at 0.79 in adolescence and early adulthood in the Canadian compared to the German study (0.82 and 0.82, respectively) and notably lower compared to the Dutch findings in adolescence (0.87), early adulthood (0.83) and later adulthood (0.73 vs 0.85). This cannot be easily explained by cultural differences as the normal birthweight (NBW) means were exactly the same in Canada and Germany in adolescence (0.88) and early adulthood (0.89) (the Dutch study had no controls). The difference is most likely due to the Canadian study investigating ELBW while the other two studies reported on more mature and larger VP/VLBW. A previous comparison of the three cohorts, focusing on ELBW indicated that at least the German and Canadian ELBW had similarly low HRQOL in adolescence (Verrips et al 2008). This comparison provides further evidence that, firstly, HRQOL of ELBW individuals is, on average, lower than that of VP/VLBW who in turn report lower HRQOL than NBW adolescents and adults. Secondly, HRQOL does not improve with age in ELBW or VP/VLBW. Thirdly, NSI reduces HRQOL well into adulthood. The stability of these differences compared to NBW indicates that whatever services ELBW or VP/VLBW individuals received from early adolescence onwards made no difference to their HRQOL in adulthood.

## DEVELOPMENTAL MECHANISMS

Understanding why VP survivors have more developmental problems and why some impairments persistent across time whilst others show plasticity is important, not just for theoretical advancement but for informing the development of interventions. Here we explore potential developmental mechanisms to help explain the lifecourse consequences of VP birth.

**Environmental influences**

Most prospective studies have used a simple main factor model investigating the association between perinatal differences at birth and adverse developmental outcomes (see **Figure 1 A,** Model 0). This approach is limited as it fails to take account of other important influences which may operate between birth and later outcomes. For illustration, we will consider three such factors: socio-economic status (SES), parenting quality and traumatic peer influences. These factors are located in different layers in Bronfenbrenner's ecological model (Bronfenbrenner 1989) and may operate in different ways in conjunction with VP birth and associated complications.

INSERT FIGURE 1 A,B here

Firstly, these factors may have a *main effect* on VP children's development (see **Figure 1,** Model 1). For example, SES may be an additional factor predicting developmental outcome. It also means that the effects of low SES are the same for children born VP and at term, and are additive. If low SES has detrimental effects on the outcome under consideration, then low SES would be considered as a risk factor. Conversely, if high SES has beneficial effects, then it could be considered a protective factor (Luthar et al 2000).

Alternatively, SES may be a *moderator* of the association between VP birth and the outcome of interest (**Figure 1 A;** Model 2). This means, for example, that low SES has a significantly larger effect in VP children, i.e. they are more vulnerable to the effects of SES than children born at term, consistent with a diathesis-stress model (Ellis et al 2011).

Furthermore, if high SES provides protection against the effects of VP birth and children reach the level of functioning of those born at term, then this would be considered resilience - the ability to bounce back after exposure to risk (i.e., VP birth) (Taylor et al 2019).

Let us consider the main factor and moderation models within the context of findings from cohort studies. It has been shown that being born into a high SES versus low SES family has a similar effect on child (Wolke & Meyer 1999) and adult IQ (Eryigit Madzwamuse et al 2015) in VP and term-born populations. The effects of SES on IQ is comparable to the effect of being born VP versus term in effect size (Eryigit Madzwamuse et al 2015). Expressed differently, having a mother whose highest educational attainment was at elementary/secondary school has the same adverse effect on IQ as having suffered severe brain damage or chronic lung disease (Benavente-Fernández et al 2019). These findings are consistent with a main factor model with no indication of an interaction effect (**Figure 1 A,** Model 1). It is thus no surprise that SES is reported as one of the major influences on cognitive outcomes in VP children (Breeman et al 2017, Linsell et al 2015). It is, however, disconcerting that, by 2018, only 15 of 70 studies included in a meta-analysis of VP birth and IQ considered some marker of SES (Twilhaar et al 2018a).

SES reflects a multitude of factors including social, family and parenting factors (Wolke 2019) that need to be unpacked. If we wish to unlock the black box of how these factors influence development, we need to measure them in as much detail as we have perinatal complications (Wolke 2019) which will require greater collaboration across disciplines in the design of follow-up studies. Let us consider parenting, a factor strongly associated with SES (Sherman & Harris 2012) and academic achievement. Wolke and colleagues found that the effects of sensitivity of parenting assessed at 6 years of age were moderated by birth status (i.e., VP vs. term) (Wolke et al 2013): VP children were strongly and adversely affected by low sensitive parenting while, on the other hand, very sensitive parenting was found to lead to academic attainment nearly on a par with children born at term (see **Figure 2).** Thus the effects of VP birth on academic outcomes are moderated by sensitive parenting. This follows a diathesis-stress model and indicates potential resiliency in academic outcomes for those born VP (see **Figure 1,** Model 2).

INSERT FIGURE 2 here

Another interaction (see **Figure 1 A**, model 2) argues that variations in child characteristics may alter susceptibility to environmental influences, i.e. the sensitivity to both negative and positive influences. This differential susceptibility proposes that certain environmental influences such as parenting can lead to poorer outcome under conditions of poor parenting and to better outcomes under conditions of good parenting in susceptible compared to non-susceptible individuals (Ellis et al 2011, Ellis & Del Giudice 2019). There is little reason to suggest that VP birth may be related to vantage sensitivity, i.e. increased sensitivity to positive experiences (Belsky & Pluess 2013). From an evolutionary perspective, most of these infants without modern NICU care would not have survived. Indeed, when Diathesis-stress versus Differential Susceptibility Theory (DST) were tested in LBW children, there was little evidence for DST but support for the Diathesis-stress model (Jaekel et al 2015). Thus, there is increasing evidence that VP birth makes children more vulnerable to environmental risk factors (Poehlmann et al 2015, Van Lieshout et al 2018a, Wolke 2018).

A third model considers environmental factors as *mediators* between VP birth and later outcomes (see **Figure 1**, Model 3). VP children, as reviewed, are at higher risk for emotional problems in adolescence. Similarly, it is well documented that children who are exposed to trauma, such as being bullied by peers, are at higher risk for emotional problems (Wolke & Lereya 2015, Zwierzynska et al 2013). In a recent investigation it was noted that a major part of the effect of EP/VP birth on emotional problems was explained by EP/VP children being more than twice as likely to be bullied than their term-born peers, which in turn explained the excess of emotional problems in adolescence. Thus bullying completely mediated the effects of EP/VP birth on emotional problems (Wolke et al 2015a).

**Genetic influences**

Preterm birth is an environmental event that sets off a cascade of further environmental interventions, i.e. NICU care. In all children, genes are involved in cognitive or behavioral development. Thus genetically sensitive designs ranging from twin studies to the use of genome wide association studies (GWAS) based on polygenic risk scores may be used to determine genetic contributions to developmental outcomes. Effects of genes are dependent on whether they can be expressed, or whether shared or non-shared environmental factors, i.e. neonatal complications or brain injury, reduce their expression. Indeed, it was found that in VP children any additive genetic effects were overshadowed by shared environmental factors in twin pairs (Koeppen-Schomerus et al 2000). More than 85% of the variance in cognitive scores at 2 years of age was explained by shared environment, thus gene effects may be much reduced compared to birth at term, at least in early development.

Twin designs can further help to test causal links using twin pairs that are discordant for a risk factor. Groen-Blokhuis and colleagues (Groen-Blokhuis et al 2011) tested three models using mono-zygotic (MZ) and dizygotic (DZ) twin pairs and unrelated (UR) individuals discordant for birthweight. Their findings showed clearly that low birthweight rather than shared genetic effects was a causal factor for higher attention problems. Unfortunately, whilst babies can be discordant for birthweight, gestation rarely varies and thus effects of gestation cannot be tested within such designs. Future research including polygenic scores may serve to evaluate how VP birth as an environmental event may reduce genetic effects.

**The Brain**

VP birth confers an insult to normal brain development (i.e., interrupted development) and there is often the superimposed risk of acquired brain injury (e.g. haemorrhage) (Volpe 2009). At the limits of survival (22-24 weeks' gestation), the brain consists entirely of white matter. In the following 16 weeks, grey matter expands rapidly with a dramatic increase in brain surface area through cortical folding (Hüppi et al 1996, Kapellou et al 2006). When babies are born prematurely, this pattern of growth is disrupted either due to alteration in growth patterns, direct injury to the white matter (Constable et al 2008, Inder et al 2005, Miller et al 2005) or for as yet to be determined reasons. The earlier the birth, the greater the disruption and in addition, boys are affected more than girls (Kapellou et al 2006, Vasileiadis et al 2009). This leads to building a different brain with altered grey and white matter distribution in multiple regions indicating reorganization of cortical and subcortical structures relating to brain volume, volume distribution, microstructure and connectivity (Ball et al 2013). These alterations are still detectable in adulthood in many areas (Bäuml et al 2015, Meng et al 2016).

Recent advances in neuroimaging have taken two directions. Firstly, the development of MRI-compatible incubators with integrated head coil that allow for sequential scanning of the developing brain while in neonatal intensive care (Hintz & O'Shea 2008). Secondly, the routine availability of MRI to allow the study of anatomical differences and, more recently, functional MRI studies to understand differences in brain area activation and connectivity in ex-preterm children and adults (Nosarti 2013).

A crucial pathway will be to determine how changes in brain development due to VP birth are associated with functional outcomes such as cognitive, emotional or social development (Montagna & Nosarti 2016) (See **Figure 1 B**, brain alterations as mediator of effects). Such outcomes may be related to anatomical alterations (Nosarti et al 2008), whole network alterations (Kelly et al 2015, Meng et al 2016) or to specific alterations such in the cholinergic forebrain (Grothe et al 2017), and may be potentially treatable. Early studies were promising and showed significant associations between early brain development assessed during the neonatal period and delayed development 2 years later (Kapellou et al 2006). However, more than a decade on, comparison of costly MRI versus the utility of cranial ultrasound are sobering. In a recent study, MRI predicted adverse motor outcomes slightly better than ultrasound, but both methods were insensitive and neither predicted cognitive problems at age 18-24 months (Edwards et al 2018). A mild beneficial effect of MRI was found in that parents liked MRI and seeing the whole brain and that reduced their anxieties more than an ultrasound. However, a single MRI in the UK costs approximately £300 more than routine ultrasound. Furthermore, social factors have been found to alter brain development and have to be considered in studies (Kim et al 2018). Furthermore, simply measuring head size in the first years of life is highly correlated with brain growth and is predictive of later cognitive development (Jaekel et al 2018b). Thus, it is important to consider what measures are required for basic science to advance knowledge of developmental mechanisms and which are sufficient for routine follow-up (Doyle Lw 2014).

In summary, to understand how VP birth leads to adverse outcomes, it is necessary to have more detailed measurement of environmental influences. Furthermore, for different outcomes and environmental factors, different mechanisms and models may apply. Understanding how VP birth alters brain development and how environmental experiences such as trauma or parenting get into the brain may help to understand the neural mechanisms underlying phenotypic behavior.

## CONCLUSIONS AND FUTURE DIRECTIONS

First, VP birth has a wide range of adverse effects on motor and psychological development and wellbeing across the lifespan. **Figure 3** summarizes the effects of VP/VLBW birth on functioning across the various domains reviewed. It shows the approximate size of the effects as reported across studies in childhood and in adulthood. Effect sizes are defined as small (OR 1.48 or inverted .67; Cohen's d between means: 0.2), moderate (OR: 3.45 or 0.29; Cohen's d: 0.5) or large (OR: 9 or 0.11; Cohen's d: 0.8) (Cohen, 1988).

INSERT FIGURE 3 here

The largest adverse effects of VP compared to FT are found for CP, DCD, IQ and ASD. While the effect sizes are large, CP is found in less than 5% of VP/VLBW, ASD in 7-8% but DCD and, in particular, low IQ (< -2 SD) in up to 25% of VP children. Thus DCD and IQ are the major sequelae of VP birth. VP/ birth has further moderate effects on academic attainment, in particular lower mathematics and spelling scores, the higher need for SEN in school, increased risk of any psychiatric disorder in childhood, in particular, for ADHD. Furthermore, moderate effect sizes were found for executive functions and personality such as being less extraverted, more neurotic and less likely to engage in risk-taking behavior. Small effect sizes were found for internalizing and externalizing problems, relationship with peers, bullying and HRQoL in childhood. While the effect sizes are small for the latter, these usually affect a large proportion of VP individuals. Relationship with parents are little affected in regards to parental sensitivity and the effects for overprotection are either small or may be explained by VP/VLBW higher needs for framing due to lower IQ.

Secondly, some adverse effects reduce across development and others persist from childhood into adulthood. Intelligence and executive functioning show no or very little improvement with age into adulthood. Social difficulties noticed in childhood in ASD symptoms and relationships with peers are still found in adulthood manifest in a withdrawn personality and less engaging in normative risk-taking behaviors. Overall, the risk of psychiatric disorders seems to reduce by adulthood (see **Figure 3**). The motor, cognitive, emotional and social difficulties are likely to contribute to the difficulties some VP individuals have in the transition to adulthood, including being less likely to participate in higher education, employment and receiving social benefits. Most notable is their lack of romantic and sexual relationships and having children themselves. Thus, more VP than FT adults may have lower social and financial support once their parents are gone with important implications for future public support.

Thirdly, VP individuals who have a significant deficit in one domain (e.g., IQ), often have problems in other domains (e.g. academic achievement, social relationships). Thus co-morbidity is frequent and, for a minority of VP children and adults, the problems are complex requiring support from medical, psychological and education services. However, even term-born children rarely have no problems at all (Wolke & Meyer 1999) and thus it is important to remember that, despite the often increased odds of adverse outcome, most VP children and adults develop adaptively without major problems.

Fourthly, despite the significant decrease in mortality and CP for babies born VP, there is as yet no evidence that this has been matched by improved developmental outcome across the domains reviewed.

Regarding future perspectives, there are a range of challenges for research, practice and intervention. Firstly, much of the observational research on the effects of VP birth may be too simplistic, failing to go beyond medical factors associated with VP birth in their analysis. Developmental Science has much to contribute to help unravel what factors across life may increase risk further, provide protection or resilience, or mediate the association with life outcomes. This is unlikely to be achieved by a single profession or single longitudinal study, which is often limited in statistical power. It requires interdisciplinary collaboration, and bringing together cohort and registry studies across the world. Such ongoing collaborations include the APIC initiative (www.apic-preterm.org) and a large EU funded project, RECAP-preterm (www.recap-preterm.eu). Neuroimaging and genetic sensitive designs should also be considered for future cohort studies.

Secondly, the use of core measures across cohort studies (Doyle Lw 2014) would allow for direct comparison of whether changes in neonatal care across consecutive cohorts have led to changes in developmental outcomes. This will need to include measures of the social environment, such as parent and peer relations, as changes may be due as much to social changes as to advances in neonatal care.

Thirdly, primary prevention of preterm birth itself is needed, but such efforts have met with little success to date. Thus, a key challenge is to minimise adverse effects of VP birth on the brain during neonatal care and to promote development after discharge. As schooling is one of the major factors affecting life course outcomes, new interventions extending beyond the first two years should be trialled, including new resources to improve educational support for children born preterm (www.pretermbirth.info) (Johnson et al 2019a, Johnson et al 2015).

Finally, reports on developmental outcome of VP children into adulthood come exclusively from high income countries. However, the vast majority of preterm children are born in transitional or low income settings (Chawanpaiboon et al 2019) and we have no idea how they fare in life. This paucity of research in low income countries needs to be addressed.

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